Case Report

Hidden Peril: Euglycemic Diabetic Ketoacidosis Unveiled in three Patients Commencing SGLT2i Treatment

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Abstract

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have been widely used due to their superior cardiovascular and renal protective effects. However, euglycemic diabetic ketoacidosis could be a serious adverse effect of them. Here, we present three cases in which varying degrees of euglycemic ketoacidosis occurred after the use of SGLT2i. The first patient experienced vomiting and shortness of breath after the concurrent use of GLP-1 agonists. The second patient developed thirst and drowsiness two days post-coronary angiography and using SGLT2i. The third patient developed cardiac tamponade on the day of receiving coronary stenting, but after pericardiocentesis and drainage, the condition of the patient improved. On the third evening, the third patient exhibited ST-T changes on the electrocardiogram and experienced nocturnal respiratory distress. After treatment with insulin and fluid replacement, all three patients recovered completely. All three patients share a common characteristic: uncontrolled hyperglycemia and high glycated hemoglobin in the presence of certain triggers, such as low BMI, uncontrolled diet and invasive procedures. The onset of SGLT2-related diabetic ketoacidosis could be rapid, particularly in certain high-risk populations. SGLT2i may need to be avoided in these circumstances. It is crucial to maintain vigilance for the occurrence of this condition to recognize and treat it as early as possible.

Keywords: SGLT2i; euglycemic diabetic ketoacidosis; type 2 diabetes mellitus, uncontrolled hyperglycemia

Introduction

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) are a class of oral antidiabetic drugs that work by blocking the reabsorption of glucose in the proximal convoluted tubules of the kidneys, thereby reducing blood glucose levels. Multiple guidelines recommend the use of SGLT2i for cardiorenal protection, regardless of the presence of diabetes [1,2]. However, SGLT2i can potentially lead to euglycemic diabetic ketoacidosis (EDKA), a clinical syndrome characterized by euglycemia (blood glucose less than 250 mg/dL) in the presence of severe metabolic acidosis (arterial pH less than 7.3, serum bicarbonate less than 18 mmol/L) and ketosis [3,4]. This could be related to the mechanism of action of SGLT2i. SGLT2i increases the loss of urinary glucose, which can induce carbohydrate deprivation and volume depletion, in turn raising the glucagon/insulin ratio and causing severe dehydration and ketosis Additionally, SGLT2i can limit the renal clearance of beta-hydroxybutyrate and acetocetate [4,5]. Under certain triggering factors such as pregnancy, alcohol consumption, surgery, illness, or starvation, patients taking SGLT2i may experience ketosis [6]. Here we present three cases of varying degrees of ketosis observed soon after the use of SGLT2i. We hope
that these cases will be a great contribution to the prevention and management of SGLT2i related EDKA. The medical history of these three patients is described below (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>25.4</td>
<td>25.8</td>
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<tr>
<td>Gender</td>
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<td>M</td>
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<td>HbA1C at the time of eDKA diagnosis</td>
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<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>114.2</td>
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</tr>
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<td>SGLT2i and other medications</td>
<td>Liraglutide 0.6 mg qd, Canagliflozin 100 mg qd</td>
<td>Dapagliflozin 10 mg qd</td>
<td>Sitagliptin 5 mg qd, Metformin 500 mg bid, Acarbose 50mg tid Dapagliflozin 10 mg qd</td>
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<td>Duration of SGLT2i treatment before eDKA development (days)</td>
<td>2</td>
<td>2</td>
<td>365~</td>
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<tr>
<td>Recovery Time (days)</td>
<td>6</td>
<td>2</td>
<td>3</td>
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</tbody>
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Table 1: Patient demographics with accompanying clinical history

**Case Presentation**

Case 1 involved a 46-year-old female who was admitted to the hospital on May 4th, 2021, due to chest pain. On the same day, she received a diagnosis of type 2 diabetes with a glycated hemoglobin (HbA1c) level of 11.7%. Immediate treatment was initiated with metformin 0.5 mg twice daily and acarbose 50 mg three times daily. During the treatment, urinalysis showed 3+ glucose and 2+ occult blood, but the absence of ketones was depicted. On May 6th, metformin was discontinued due to persistent abdominal pain, and the patient was switched to canagliflozin 100 mg daily and liraglutide 0.6 mg daily. On May 7th, the patient developed severe anorexia and vomiting, leading to the discontinuation of liraglutide. Although vomiting stopped afterward, the patient’s appetite did not improve, and she exhibited poor mental status. During this period, the patient’s fasting blood glucose fluctuated between 162-198 mg/dL, and postprandial blood glucose ranged from 180-252 mg/dL. On May 9th, she experienced altered consciousness, dyspnea, and blood analysis revealed a pH of 6.89 and bicarbonate of 2.9 mmol/L (Figure 1a). The urinalysis results indicate ketones at 3+, protein at 2+, and glucose at 4+. After receiving standard treatment for diabetic ketoacidosis, she recovered on May 16th. Subsequently, she underwent insulin therapy for the next six months without further use of canagliflozin.
Figure 1a: Trend of arterial blood gas pH and Bicarbonate levels from Case 1 from discovery of EDKA to resolution. Note values denoted with asterisks indicate bicarbonate values below the measurable range (3 mmol/L).

Case 2 involved a 65-year-old female who was admitted to a nearby hospital on March 14, 2022, due to chest pain persisting for 5 days. She was diagnosed with type 2 diabetes and had an HbA1c level of 12.3%. Her fasting blood glucose levels ranged around 144-180 mg/dL, and post-prandial blood glucose levels reached a maximum of 360 mg/dL. She was initially prescribed acarbose 50 mg three times daily. On March 18, coronary angiography revealed severe stenosis in the left anterior descending artery. On the same day, dapagliflozin 10 mg once daily was added to her medication regimen post-operation. On March 19, she was transferred to our hospital for revascularization. In the early morning of March 20, the patient experienced thirst, decreased appetite, and had an episode of vomiting. Her fasting blood glucose level was 123 mg/dL. Blood analysis revealed a pH of 7.31, bicarbonate of 21.9 mmol/L, (Figure 1b) and a high anion gap of 24 mEq/L. Urinalysis revealed 3+ glucose and 2+ ketones. After receiving standard treatment for ketoacidosis, the patient recovered on March 21.
Case 3 involved a 55 year old male who was admitted to the hospital on May 11, 2023, due to dyspnea on exertion for the past 3 years. He has a history of diabetes for 10 years and was taking sitagliptin 5mg, metformin 500mg, and dapagliflozin 10mg daily for the past year. The patient had not regularly monitored his blood glucose levels for over 6 months, and his HbA1c was 8.1%. Blood glucose monitoring revealed predominantly elevated postprandial blood glucose levels, reaching a maximum of 370 mg/dL. It was recommended to control the patient’s diet and initiate insulin therapy. However, the patient insisted on using oral medications only, as a result, 50 mg of acarbose was prescribed three times daily in addition to diet controls. Postprandial blood glucose could be maintained around 160-180 mg/dL through this regimen.

On May 15th, the patient underwent coronary angiography, which revealed severe stenosis in the left anterior descending artery (LAD). The recommendation was to implant two stents in the blocked artery. The patient expressed the need for consideration and decided to postpone the procedure. On May 17th, the patient underwent stent implantation in the LAD artery. During the procedure, there was an injury to the diagonal branch. Four hours later, the patient developed dyspnea and hypotension. Bedside ultrasound revealed pericardial effusion and approximately 220 ml of bloody pericardial fluid was aspirated through pericardiocentesis. The symptoms improved following the procedure. Subsequently, the patient’s vital signs were stabilized, the diet returned to normal, ECG exhibited no abnormalities (Figure 2a), and high-sensitivity troponin (hsTNI) was normal.

On May 19th, around 5 pm, the patient experienced mild chest discomfort. A repeat bedside ultrasound did not show an increase in pericardial effusion volume, and the wall motion was normal. The electrocardiogram showed ST-segment elevation in leads V2-V9, V4r-V5r II, III, and aVF (Figure 2b). Serum electrolytes and CK-MB were within normal range but hsTNI increased to 76.5ng/L (normal range <26.2ng/l). Immediate repeat coronary angiography did not reveal any abnormalities. Intravenous nitroglycerin was administered, and the symptoms improved. In the early morning of the following day, the patient suddenly developed severe chest discomfort and dyspnea. Despite nitroglycerin administration, the patient’s hsTNI further elevated to 595ng/L. The patient was treated with diltiazem. However, the symptoms did not alleviate. Blood analysis revealed a pH of 7.272, bicarbonate of 10.3 mmol/l (Figure 1c), and an anion gap of 22.2 mEq/l. Blood lactate level was 34 mg/dL (normal range: 4.5-20 mg/dL). Blood ketone level was 127 μmol/L (normal range:200-
Blood beta-hydroxybutyrate was higher than 4.5 mmol/L (normal range: 0.02-0.27 mmol/L) exceeding the measurable value. Urinalysis showed 4+ glucose and 2+ ketones. After receiving proper treatment for ketoacidosis, the patient’s symptoms of chest tightness and shortness of breath have improved. On May 22nd, the follow-up electrocardiogram showed atrial fibrillation (Figure 2c), and the ST segment was mostly back to normal. On May 24th, the follow-up blood analysis revealed a high lactate level of 38.4 mg/dL. The blood ketone level had returned to normal at 47 μmol/L, and the blood beta-hydroxybutyrate had decreased to 2.5 mmol/L. The patient recovered on May 26th. He was discharged on June 2nd. After close follow-up in the outpatient setting, the electrocardiogram showed a restoration of sinus rhythm; however, several leads showed inverted T-waves (Figure 2d).

![Figure 1c: Trend of pH and bicarbonate for Case 3 from discovery of EDKA to resolution.](image)
Discussion
The three cases mentioned above illustrated the aftereffects of SGLT2 use. All three of the aforementioned patients were at risk for side-effects related to SGLT2 use.

EDKA may be more common in patients with diabetes using SGLT2, particularly in those with lower BMI and decreased glycogen stores [4]. Case 1 highlights the risk associated with extremely low body mass index (BMI) when using SGLT2. Furthermore, the combination therapy of GLP-1 receptor agonists and SGLT2 may lead to an increased risk of gastrointestinal discomfort, nausea, vomiting, and diarrhea. Therefore, healthcare professionals and patients should closely monitor signs and symptoms of gastrointestinal reactions and ketosis when using the combination therapy of GLP-1 receptor agonists and SGLT2 for type 2 diabetes.

The latest guidelines have suggested discontinuing SGLT2 3 to 4 days before invasive surgery [7]. However, as seen in case 2, SGLT2 was initiated following coronary angiography on the same day as the procedure, and ketosis symptoms occurred on the third day of medication, despite having a normal diet during this period. This situation highlights the need for increased caution and consideration regarding the management of SGLT2 both before and after a semi-invasive procedure.

In case 3, we observed that even in patients who are generally in good health and maintaining a normal diet and have been taking SGLT2 regularly for a significant time, hidden diabetic ketoacidosis (DKA) can still occur, especially after percutaneous coronary intervention and resulting cardiac tamponade as a complication of stent implantation. In the early stages, the patient did not exhibit respiratory distress or gastrointestinal symptoms. Instead, only ST-segment elevation was observed on the routine electrocardiogram, despite having a normal diet during this period. This situation highlights the need for increased caution and consideration regarding the management of SGLT2 both before and after a semi-invasive procedure.

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